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# Impaired Systolic Blood Pressure Recovery and Heart Rate Recovery After Graded Exercise in Patients With Metabolic Syndrome

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**Abstract:** The aim of this study was to evaluate and compare systolic blood pressure recovery and heart rate recovery (HRR) values obtained at various time intervals after maximal graded exercise treadmill testing between patients with metabolic syndrome (MS) and the controls without MS. To our knowledge, this is the first study indicating systolic blood pressure recovery (SBPR) impairment and its relations to HRR and other variables in this group of patients.

The study population included 110 patients with MS (67 men, 43 women; mean age:  $46 \pm 9$  years) and 110 control subjects who did not meet the criteria for MS (58 men, 52 women; mean age:  $44 \pm 10$  years). All patients were selected from nonobese, apparently healthy sedentary individuals who had the ability to perform maximum exercise testing. SBPR was assessed by calculating the ratio of systolic blood pressure (SBP) obtained in the third minute of the recovery period to either the peak-exercise SBP or the SBP in the first minute of the recovery period after graded exercise testing. HRR values were calculated by subtracting the HR at the first, second, third, fourth, and fifth minutes of the recovery period from the HR reached at peak exercise.

There was no significant difference found between the 2 groups with respect to age and sex distribution. As expected, patients with MS had higher waist circumference, fasting plasma glucose and serum triglyceride, and lower high-density lipoprotein cholesterol compared with control subjects. All HRR values calculated in the first, second, third, fourth, and fifth minutes were significantly detected lower in the MS group compared with the control group (HRR 1st:  $32 \pm 10$  vs  $36 \pm 11$ ;  $P = 0.009$ ; HRR 2nd:  $47 \pm 10$  vs  $51 \pm 11$ ;  $P = 0.02$ ; HRR 3rd:  $53 \pm 11$  vs  $58 \pm 12$ ;  $P = 0.001$ ; HRR 4th:  $57 \pm 11$  vs  $64 \pm 12$ ;  $P < 0.001$ ; HRR 5th:  $60 \pm 16$  vs  $69 \pm 15$ ;  $P < 0.001$ ). In addition, calculated mean values for SBPR1 and SBPR2 were  $>1$  in patients with MS ( $1.01 \pm 0.2$  vs  $0.91 \pm 0.1$  and  $1.01 \pm 0.1$  vs  $0.94 \pm 0.1$ ) and these were statistically significant compared with the control group ( $P < 0.001$  and  $P = 0.002$ , respectively). The existence of MS was found to be the only parameter that was independently and positively related to SBPR values in the study population.

Our findings suggest that only the existence of MS itself, not the presence of any MS components, is independently associated with SBPRs. We are of the opinion that significantly impaired SBPR values, in addition to the decreased HRR values observed in this group of patients, such as those with MS, may especially help identify patients with potentially increased cardiovascular risk despite normal exercise stress testing findings.

(*Medicine* 94(2):e428)

**Abbreviations:** BMI = body mass index, BP = blood pressure, CAD = coronary artery disease, DBP = diastolic blood pressure, HDL = high-density lipoprotein, HR = heart rate, HRR = heart rate recovery, LDL = low-density lipoprotein, MS = metabolic syndrome, SBP = systolic blood pressure, SBPR = systolic blood pressure recovery.

## INTRODUCTION

Systolic blood pressure recovery (SBPR) is defined as the ratio of the systolic blood pressure (SBP) obtained in the third minute of the recovery period to either the peak-exercise SBP<sup>1</sup> or the SBP in the first minute<sup>2</sup> of the recovery period after graded exercise testing. It was first reported in the literature that a delay in the decrease of SBP after exercise was more accurate than ST segment depression for the diagnosis of coronary artery disease (CAD).<sup>3</sup>

Delayed heart rate recovery (HRR), which is defined as the difference in heart rate (HR) at peak exercise and HR at a specific time interval following the onset of recovery, appears to be associated with the balance of sympathetic and parasympathetic tonus. In addition, HRR is a reflection of vagal reactivation and impaired HRR is considered to represent decreased vagal tone.<sup>4,5</sup> Autonomic dysfunction including impaired vagal reactivation as well as sympathetic overactivity is known to be associated with metabolic syndrome (MS).<sup>6–8</sup>

The aim of this study was to evaluate and compare SBPR and HRR values obtained at various time intervals after maximal graded exercise treadmill testing between patients with MS and the controls without MS. To our knowledge, there is no data previously published in the literature about SBPR values observed in patients with MS and the relationship between HRR and SBPR values in this group of patients.

## METHOD

### Study Population

The study population included 110 patients with MS (group I, 67 men, 43 women; mean age,  $46 \pm 9$  years) and 110 control subjects who did not meet the criteria for MS (group II, 58 men, 52 women; mean age,  $44 \pm 10$  years). All patients were selected from nonobese, apparently healthy sedentary

Editor: Hsueh hwa Wang.

Received: November 17, 2014; revised: December 2, 2014; accepted: December 4, 2014.

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The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000000428

individuals who had the ability to perform maximum exercise testing. In order to avoid the effect of manifest ischemia on HRR and BPR values, only patients whose exercise tests terminated due to reaching target HR were taken into analysis. All other reasons for termination of exercise, such as marked ST depression ( $>2.5$  mm), ventricular tachycardia, exercise SBP  $>250$  and/or diastolic blood pressure (DBP)  $>110$  mm Hg, and limiting symptoms resulted in exclusion of patients from the study.

Exclusion criteria included known CAD, history of myocardial infarction, left ventricular dysfunction, cardiomyopathy, congenital heart disease, left ventricular hypertrophy, valvular heart disease, an implanted pacemaker, preexcitation syndrome, atrial fibrillation, hypothyroidism or hyperthyroidism, hypertension, chronic respiratory disease, malignancy, and orthopedic or musculoskeletal disorders. The use of any medications affecting blood lipid profile, glucose level, blood pressure (BP), and HR response to the exercise were also accepted as exclusion criteria. An additional exclusion criteria was participants' failure to augment SBP by at least 10 mm Hg above their resting BP to eliminate those with hypotensive or markedly blunted BP response to exercise, which indicate a greater likelihood of severe CAD. Besides, patients with a maximum SBP  $\geq 220$  and/or maximum DBP  $\geq 100$  mm Hg, indicating exercise-induced hypertension,<sup>9</sup> were also excluded from the study. This study was prospectively designed; it was prepared in accordance with the Declaration of Helsinki and was approved by the local Ethic Committee of Pamukkale University medical faculty. An informed consent was taken from all the patients.

## Medical Examination

Seated BP and HR were measured in a quiet room 3 times after a 5 minutes rest with the average of the last 2 measurements. Height and weight values were measured with the participants in light examination clothes without shoes. Waist circumference was measured using the average of 2 measurements between the iliac crest and the bottom of the ribcage while the subject was standing. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters. The lipid profiles and glucose level were measured by using routine laboratory techniques after at least 12 hours of fasting.

## Definition of MS

We defined MS according to the definition of the "Third Adult Treatment Panel"<sup>10</sup> as being present if  $\geq 3$  of the following components were met: fasting blood glucose level  $\geq 110$  mg/dL; SBP  $\geq 130$  or DBP  $\geq 85$  mm Hg; triglyceride level  $\geq 150$  mg/dL; high-density lipoprotein cholesterol level  $\leq 40$  mg/dL in men or  $\leq 50$  mg/dL in women; and waist circumference  $>102$  cm in men or  $>88$  cm in women.

## Protocol of the Exercise Stress Test

The patients underwent a standard maximal graded exercise treadmill test according to the standard Bruce protocol with a Quinton Treadmill system (Quinton Inc., Bothell, WA). Continuous, 12-lead electrocardiographic monitoring was performed throughout testing. The Tango exercise BP monitoring device (SunTech Medical, Morrisville, NC) was used to automatically measure each subject's BP and HR before and at the second minute of each stage of the exercise. The participants exercised until the HR achieved was  $>95\%$  of estimated maximal HR ( $220 - \text{age}$ ). The patients continued to walk for 60 seconds at a speed of 1.5 mph during the recovery period,

after which they sat down with continued BP and HR monitoring. HRR values were calculated by subtracting the HR at the first, second, third, fourth, and fifth minutes of the recovery period from the HR reached at peak exercise. SBP recovery was assessed by calculating the ratio of SBP obtained in the third minute of recovery period to the peak-exercise SBP (SBPR1) after graded exercise. Because it has been noted that BP measurement obtained by indirect sphygmomanometry during exercise may be subject to a high degree of error, even as much as 40 mm Hg at peak exercise,<sup>11</sup> we also assessed the decline in SBP by calculating the ratio of SBP obtained in the third minute of recovery period to SBP in the first minute of recovery period (SBPR2). Therefore, we especially preferred SBPR2 as our index of SBPR because of both SBPs having been measured only in the recovery state. A value  $>1$  for these measurements was considered abnormal in accordance with the literature.<sup>2</sup> The exercise capacity was calculated as total metabolic equivalent units (METs) achieved at peak exercise.

## Statistical Analysis

While continuous variables were expressed as mean  $\pm$  SD, categorical variables were expressed as percentages. Comparisons of categorical and continuous variables between the 2 groups were performed by using the  $\chi^2$  test and unpaired  $t$  test, respectively. The correlation between various parameters, HRR and SBPR values, was evaluated by the Pearson correlation test. Multivariate linear regression analysis was applied to evaluate the effects of various parameters on SBPR2. A  $P$  value of  $<0.05$  was regarded as statistically significant. The SPSS (SPSS Inc., Chicago, IL) version 17.0 statistical package was used for all analyses.

## RESULTS

There was no significant difference found between the 2 groups in respect to age and sex distribution. Resting HR, the status of cigarette smoking, total cholesterol level, and height values were also similar between the 2 groups. However, patients with MS had higher weight and BMI values compared with controls. As expected, patients with MS had higher waist circumference, fasting plasma glucose and serum triglyceride, and lower HDL cholesterol compared with the control subjects. Patients with MS had a higher LDL cholesterol level as well. Additionally, preexercise SBP was significantly higher in the MS group compared with the control patients ( $P=0.002$ ). Baseline clinical characteristics of patients with MS and control patients are presented in Table 1.

Peak SBP and recovery SBP values at the first and third minutes were found to be statistically higher in patients with MS ( $P<0.001$ ). All HRR values calculated were significantly detected lower in the MS group compared with the control group (HRR 1st:  $32 \pm 10$  vs  $36 \pm 11$ ;  $P=0.009$ ; HRR 2nd:  $47 \pm 10$  vs  $51 \pm 11$ ;  $P=0.02$ ; HRR 3rd:  $53 \pm 11$  vs  $58 \pm 12$ ;  $P=0.001$ ; HRR 4th:  $57 \pm 11$  vs  $64 \pm 12$ ;  $P<0.001$ ; HRR 5th:  $60 \pm 16$  vs  $69 \pm 15$ ;  $P<0.001$ ). In addition, calculated mean values for SBPR1 and SBPR2 were  $>1$  in patients with MS ( $1.01 \pm 0.2$  vs  $0.91 \pm 0.1$  and  $1.01 \pm 0.1$  vs  $0.94 \pm 0.1$ ) and these were statistically significant compared with the control group ( $P<0.001$  and  $P=0.002$ , respectively). Comparison of exercise test characteristics between the 2 groups is shown in Table 2.

In the MS group, there was no correlation demonstrated between any components of MS and SBPRs. There was also no association between SBPRs and smoking status, METs

**TABLE 1.** Demographic and Laboratory Findings of the Patients With Metabolic Syndrome and the Controls

	Control Group n = 110	Metabolic Syndrome n = 110	P Value
Age, y	44 ± 10	46 ± 9	0.09
Male gender, n (%)	67(60)	58 (53)	0.11
Smoking, n (%)	27 (24)	20(18)	0.16
Height, m	169 ± 18	166 ± 10	0.15
Weight, kg	75 ± 13	81 ± 13	<b>0.001</b>
Body mass index, kg/m <sup>2</sup>	26 ± 2	28 ± 2	<b>&lt;0.001</b>
Waist circumference, cm	76 ± 11	97 ± 10	<b>&lt;0.001</b>
Preexercise SBP, mm Hg	119 ± 10	125 ± 14	<b>0.002</b>
Preexercise DBP, mm Hg	81 ± 17	83 ± 12	0.33
Resting HR, beats/min	89 ± 15	92 ± 12	0.09
Fasting glucose, mg/dL	95 ± 9	109 ± 20	<b>&lt;0.001</b>
Total cholesterol, mg/dL	153 ± 102	177 ± 76	0.55
LDL cholesterol, mg/dL	99 ± 70	130 ± 44	<b>&lt;0.001</b>
HDL cholesterol, mg/dL	53 ± 11	43 ± 20	<b>&lt;0.001</b>
Triglyceride, mg/dL	101 ± 97	134 ± 86	<b>0.009</b>

DBP = diastolic blood pressure, HDL = high-density lipoprotein, HR = heart rate, LDL = low-density lipoprotein, SBP = systolic blood pressure.

value, resting HR, age, and gender. Besides, no correlation was detected between any HRR measurements and SBPRs, as well. On the contrary, the existence of MS was the only parameter that had a statistically significant correlation with both SBPR values in the entire study population. Table 3 reveals correlations between SBPR values and the other variables in patients with MS.

In addition, all the variables except for existence of MS remained unpredictable for both SBPR values after adjusting for each other ( $r = 0.22$  and  $P = 0.03$  for SBPR 1, and  $r = 0.16$  and  $P = 0.04$  for SBPR 2). Tables 4 and 5 show a multiple regression analysis results for SBPR1 and SBPR 2, respectively, in the study population.

## DISCUSSION

In this study, we have observed the following. First, all calculated HRR values were impaired in patients with MS compared with a control group who did not meet the diagnostic

criteria for MS. Second, both calculated SBPR values were found to be significantly higher in the MS group compared with the controls. Finally, we also found that existence of MS was the only independent predictor of impaired SBPRs in patients with MS. To our knowledge, this is the first study indicating SBPR impairment and its relations to HRR and other variables in patients with MS.

Clinical evaluation of SBPR as a prognostic tool for diagnosing various cardiovascular abnormalities in patients undergoing exercise testing has received considerable attention and a delay in SBPR was shown to be associated with increased risk of CAD, angina pectoris, hypertension, acute myocardial infarction, and stroke in these studies.<sup>2,12–15</sup> It was also reported that a delay in decline of SBP after exercise was more accurate than ST segment depression for the diagnosis of CAD.<sup>16</sup> Changes in SBPR are thought to be due to changes in sympathetic and parasympathetic activities,<sup>14,15</sup> systemic vascular resistance,<sup>1,15</sup> and baroreflex sensitivity.<sup>17</sup> Additionally, SBPR has also been reported to be associated with age and gender

**TABLE 2.** Comparison of Exercise Test Characteristics Between 2 Groups

	Control Group n = 110	Metabolic Syndrome n = 110	P Value
Exercise capacity (METs)	9.7 ± 1.8	9.7 ± 1.8	0.98
Peak exercise HR, beats/min	156 ± 13	153 ± 14	0.08
Peak SBP, mm Hg	139 ± 24	153 ± 25	<b>&lt;0.001</b>
Peak DBP, mm Hg	82 ± 14	84 ± 14	0.85
Recovery SBP 1st min, mm Hg	136 ± 25	150 ± 21	<b>&lt;0.001</b>
Recovery SBP 3rd min, mm Hg	129 ± 20	142 ± 18	<b>&lt;0.001</b>
SBPR1	0.91 ± 0.1	1.01 ± 0.2	<b>&lt;0.001</b>
SBPR2	0.94 ± 0.1	1.01 ± 0.1	<b>0.002</b>
HRR 1st min, beats/min	36 ± 11	32 ± 10	<b>0.009</b>
HRR 2nd min, beats/min	51 ± 11	47 ± 10	<b>0.02</b>
HRR 3rd min, beats/min	58 ± 12	53 ± 11	<b>0.001</b>
HRR 4th min, beats/min	64 ± 12	57 ± 11	<b>&lt;0.001</b>
HRR 5th min, beats/min	69 ± 15	60 ± 16	<b>&lt;0.001</b>

DBP = diastolic blood pressure, HR = heart rate, HRR = heart rate recovery, METs = metabolic equivalent units, SBP = systolic blood pressure, SBPR = systolic blood pressure recovery.

**TABLE 3.** Correlation Between Mean SBPR Values and the Other Variables in Whole Study Population

	SBPR1		SBPR2	
	Correlation Coefficients (r)	P Value	Correlation Coefficients (r)	P Value
Age	0.09	0.18	0.02	0.73
Gender	−0.02	0.76	0.03	0.58
Smoking status	−0.00	0.93	0.02	0.68
Body mass index	0.12	0.06	0.17	0.06
Waist circumference	0.04	0.66	0.05	0.47
Fasting glucose	0.09	0.17	0.07	0.25
HDL cholesterol	−0.05	0.40	−0.08	0.19
Triglyceride	−0.03	0.65	0.10	0.13
Preexercise SBP	0.13	0.05	0.09	0.16
Preexercise DBP	0.02	0.69	0.01	0.95
Exercise capacity (METs)	−0.04	0.53	0.06	0.38
Resting HR	0.02	0.75	0.04	0.53
HRR 1st min	0.00	0.91	−0.06	0.38
HRR 2nd min	0.00	0.93	−0.03	0.62
HRR 3rd min	0.02	0.75	−0.06	0.34
HRR 4th min	−0.00	0.98	−0.04	0.55
HRR 5th min	−0.04	0.52	−0.03	0.61
Existence of MS	0.25	<b>&lt;0.001</b>	0.20	<b>0.002</b>

DBP = diastolic blood pressure, HDL = high-density lipoprotein, HR = heart rate, HRR = heart rate recovery, METs = metabolic equivalent units, MS = metabolic syndrome, SBP = systolic blood pressure, SBPR = systolic blood pressure recovery.

differences, physical fitness, and HR recovery.<sup>14,18,19</sup> In another study, some independent relationships were indicated between SBPR and the other variables known to associate with cardiovascular abnormalities such as age, waist circumference, BMI, resting HR, physical activity, and smoking in at least 1 gender-specific group of apparently healthy adults.<sup>20</sup> In the present study, we have collected our data from middle-aged, apparently healthy, individuals with a similar sex and age distribution, and we found that SBPR values were significantly impaired in the MS group. However, the existence of MS was found to be the only parameter that was independently and positively related to SBPR values in the study population.

Level of physical activity has been previously associated with SBP responses to exercise<sup>21</sup> and is generally accepted as a very important risk factor for cardiovascular diseases. The rate at which SBP declines after exercise is considered to be a

reflection of a person's level of physical activity and fitness. A greater decrease in SBP from peak exercise to recovery may reflect good physical fitness and aerobic capacity.<sup>14</sup> This may be connected with the effect of exercise training in improving vascular endothelial functions and vasodilatory capabilities resulting in a decrease in systemic vascular resistance.<sup>22,23</sup> Besides, insulin resistance, dyslipidemia, as well as visceral obesity were shown to be associated with endothelial dysfunction and abnormal cardiac autonomous modulation; these parameters may be involved in inappropriate elevation of BP during exercise.<sup>24,25</sup> In the present study, although there was no statistically significant difference detected in terms of exercise capacity between the 2 groups, and both study and control groups had good exercise capacity, both SBPR values were observed to be significantly blunted in the MS group. Therefore, we thought that autonomic and endothelial

**TABLE 4.** Multiple Linear Regression Analysis Shows the Role of Metabolic Syndrome Existence and Various Parameters on Systolic Blood Pressure Recovery-1 Value in Whole Study Population

	Coefficients (r)	P Value
Body mass index	−0.02	0.77
Waist circumference	0.09	0.41
Resting HR	−0.00	0.92
Exercise capacity (METs)	−0.02	0.76
Smoking status	0.03	0.63
Existence of MS	0.22	<b>0.03</b>

HR = heart rate, METs = metabolic equivalent units, MS = metabolic syndrome.

**TABLE 5.** Multiple Linear Regression Analysis Shows the Role of Metabolic Syndrome Existence and Various Parameters on Systolic Blood Pressure Recovery-2 Value in Whole Study Population

	Coefficients (r)	P Value
Body mass index	0.10	0.16
Waist circumference	0.27	0.78
Resting HR	0.03	0.60
Exercise capacity (METs)	0.08	0.31
Smoking status	0.04	0.54
Existence of MS	0.16	<b>0.04</b>

HR = heart rate, METs = metabolic equivalent units, MS = metabolic syndrome.



dysfunction, which has previously been well established in patients with MS, might play an essential role in these impaired SBPR values.

The association between MS and increased risk for cardiovascular disease has been well established in the literature.<sup>26–29</sup> Slow deceleration of HR after exercise was shown to indicate autonomic dysfunction<sup>30</sup> and was found to be an independent predictor of cardiovascular disease and all-cause mortality.<sup>31,32</sup> It was indicated that MS has added significant prognostic information to the previously known risk factors for cardiovascular disease.<sup>33</sup> This autonomic dysfunction, including impaired vagal reactivation as well as sympathetic overactivity, is known to be associated with hyperinsulinemia, or insulin resistance, which determines MS.<sup>6–8</sup> Additionally, an impaired HRR in the first minute after exercise testing has been shown to be a powerful predictor of overall mortality that is independent of workload, changes in HR during exercise, and the existence of myocardial perfusion defects.<sup>34</sup> It was suggested in another study that decreased HRR occurred after the presence of MS itself but not before.<sup>35</sup> It was also thought that decreased HRR in the presence of MS components is one possible mechanism by which MS is associated with increased cardiovascular disease morbidity and mortality.<sup>36</sup> It was also determined that decreased HRR was independently associated with MS after adjustment for resting HR.<sup>37</sup> In our study as well, there was no significant difference between the 2 groups in terms of both baseline and peak exercise HR values, and all calculated HRR values were significantly decreased in patients with MS compared with the controls. However, there was no correlation detected between any HRR measurements and SBPR values. Despite it being well established in the literature that impaired HRR is closely related to autonomic dysfunction, there is very limited data indicating the relationship between SBPR and the autonomic nervous system. Therefore, showing significantly impaired SBPR values in patients with MS for the first time may be meaningful in respect to pointing at autonomic dysfunction, which is known to be closely associated with MS pathophysiology.

A potential limitation of this study is as follows: as understood from mean BMI values of the study groups, the majority of the study population was overweight, and the patients with MS had greater weight and BMI values compared with the controls. We do not know the exact effect of this metabolic parameter on HRR and SBPR measurements; therefore, further studies will be needed to more accurately describe these HR and BP changes during exercise testing in MS patients with normal BMI values.

In conclusion, our findings suggest that only the existence of MS itself, not the presence of any MS components, is independently associated with SBPRs. We are of the opinion that significantly impaired SBPR values, in addition to the decreased HRR values observed in this group of patients, such as those with MS, may especially help identify patients with potentially increased cardiovascular risk despite normal exercise stress testing findings.

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